REMARKS

Upon entry of the amendments made herein, claims 1, 4, 6-7, 9-11, 13, 14, 19, 21, 23-26, 30, 32, 34-40, 56-65, 67, 68, 82, 103-112, 117-143, 145-147 and 149-158 are pending in this application with claims 14, 25, 26, 30, 34-40, 56-65, 67, 68 104-108, 111, 112, 117-143, 145-147 and 149-158 currently withdrawn from consideration. Claims 1, 32 and 82 are currently amended. Claims 2, 3, 5, 8, 12, 15-18, 20, 22, 27-29, 31, 33, 41-55, 66, 69-81, 83-102, 113-116, 144 and 148 were previously canceled. Accordingly, claims 1, 4, 6-7, 9-11, 13, 19, 21, 23, 24, 32, 82, 103, 109 and 110 are currently before the Examiner.

Claims 1 and 82 are amended to further define the invention and/or to correct inadvertent typographical errors. Claim 32 was amended to further define the invention. Support for the amendment to claim 32 can be found, *e.g.*, on page 7, lines 11-14 of the specification as filed. Accordingly, no new matter has been added.

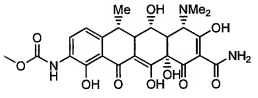
Formal Matters

Applicants acknowledge the Examiner's statement that, because no generic claims were found patentable, the claims remain restricted in scope to the elected species only (*see* Office Action at p. 2). Thus, the Examiner concluded that claims 14, 25, 26, 30, 34-40, 56-65, 67, 68, 104-108, 111, 112, 117-143, 145-147 and 149-158 are withdrawn from consideration as drawn to unelected species. *Id.*

35 U.S.C. §103

Claims 1, 7, 11, 23-25 and 67 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barden *et al.* (J. Med. Chem., 1994, v.37, no.20, p. 3205-3211) ("Barden") in view of Silverman, R. B. (The Org. Chem. Of Drug Design and Drug Action, Academic Press, Inc., San Diego, 1992, p. 4-51) ("Silverman").

The Examiner stated that Table 1 of Barden shows that compound 12,



, exhibits antibacterial activity against *S. aureus* and further indicates an activity of ">32" with respect to *E. coli* (*see* Office Action at p. 3). The Examiner also alleged that Barden suggests that alkyl homologs of compound 12 also possess antibacterial activity. *Id.* The Examiner further noted that one of ordinary skill would expect compound 12 to have some antibacterial activity for *E. coli* due to its indicated activity of ">32" in Table 1 (*see* Office Action at p. 4). Finally, the Examiner asserted that alkyl homologs are reasonably expected to possess similar activity. *Id.* Applicants traverse.

Barden's compound 12 exhibits no antibacterial activity against gram negative bacteria (*i.e.*, *E. coli* strains). However, the currently claimed compounds are effective against both gram positive and gram negative bacteria, and therefore, possess superior properties and not similar properties (*see* data showing antibacterial activity against both gram positive and gram negative bacteria at *e.g.*, Example 2 and Table 2 of the specification as filed).

The Examiner stated that Table 1 of Barden shows compound 12 as exhibiting antibacterial activity towards *E. coli* (*i.e.*, >32 μg/mL) (*see* Office Action at p. 3). Applicants note the following:

- Barden describes *E. coli* as representative of gram-negative bacteria (*see* p. 3206, right column, lines 28-33);
- Barden describes a minimum inhibitory concentration (MIC) range of 32-0.004 μg/mL in the experimental methods (*see* p. 3206, right column, lines 24-26);
- Barden reports the activity of compound 12, with respect to *E. coli*, is greater than 32 μg/mL, and therefore is outside the range (0.004-32 μg/mL) asserted by Barden as indicative of antibacterial activity.

Thus, Barden describes compound 12 as inactive against *E. coli*. As a result, Barden fails to teach that compound 12 is active against *E. coli*, and thus, Barden fails to teach that compound 12 is active against gram-negative bacteria in general.

The Examiner acknowledges Applicants' reference to *Eisai Inc. v. Dr. Reddy's Laboratories, Inc. and Teva Pharmaceuticals USA, Inc* (Fed. Cir. 2008) and highlights the following with respect to obviousness: "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship…to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." In the instant case, the Examiner asserted that compound 12 shares a sufficiently close relationship to the claimed compounds to create an expectation that the claimed compounds have similar properties to compound 12. Applicants traverse.

Applicants have shown that the claimed 9-carbamate substituted tetracycline compounds are effective against both gram positive and gram negative bacteria (*see e.g.*, Example 2 and Table 2 of the instant specification). Specifically, 9-alkylcarbamate substituted compounds M, AA, AP, AS, BQ, BR and BV exhibit activity against several bacterial strains, including a gram negative bacterium, *E. coli*, and several gram positive bacteria. Barden's compound 12 is active against gram positive species (*i.e.*, *S. aureus* strains) but not gram negative strains (*see supra*). Thus, contrary to the Examiner's assertion, the claimed compounds have superior antibacterial properties, and not similar properties, relative to compound 12.

Furthermore, Barden does not provide sufficient motivation or any objective reason to select and/or modify compound 12 to arrive at the currently claimed compounds. Contrary to the Examiner's assertion that compound 12 is one of the most effective compounds for *S. aureus* (*see* Office Action at p. 3), many other compounds described in Table 1 of Barden show superior or similar properties to those of compound 12 (*see e.g.*, compounds 4a, 4e, 14, 15 and 16).

Moreover, Barden describes 9-glycylamido-substituted doxycycline derivatives as preferred compounds throughout the reference. Barden's discussion of the data presented in Table 1 concludes with a statement of the superior properties exhibited by *N,N*-dialkylglycinamide compounds, not carbamates: "*N,N*-dialkylglycinamides exhibited maximal activity, and that activity was retained by a variety of nitrogen substituents" (*see* Barden at p. 3207, left column, lines 2-4). If anything, one would select a 9-glycylamido-substituted doxycycline derivative as a starting point for modification. Indeed, Barden's discussion of data from Table 1 fails to even mention compound 12.

In view of the above, one of ordinary skill would not have selected compound 12 as a candidate for further modification and/or study. Thus, it would not have been obvious to single out the particular compound (compound 12) identified by the Examiner, let alone to select this compound for use in the treatment of a tetracycline responsive state.

In addition, Barden does not provide sufficient motivation or any objective reason to modify compound 12 to arrive at the claimed invention. Barden teaches that lengthening the alkyl chain of the *N*-alkylglycinamide group at the 9-position results in increased potency of the described tetracycline compounds (compounds 17, 18 and 21 in Table 1). None of these compounds include a 9-carbamate substituted tetracycline structure. Moreover, Table 1 does not include sufficient data to draw a comparative conclusion with respect to 9-carbamate tetracyclines, as only one 9-carbamate tetracycline structure (compound 12) is described. Thus, even if one chose compound 12 of Barden (Applicants assert one of ordinary skill would not), there is no motivation to modify this compound to reach the compounds of the instant invention.

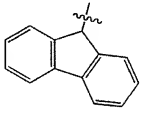
Silverman does not cure the deficiencies of Barden. The Examiner cites Silverman and Barden as evidence that alkyl homologs are reasonably expected to possess similar activity. However, the pending claims do not recite alkyl homologs of compound 12. Moreover, as discussed *supra*, the claimed compounds have superior properties, and not similar properties, relative to compound 12. Further, the currently claimed 9-carbamate substituted tetracycline compounds are chemically unrelated to the single-ring aromatic compounds described in Silverman. As a result, one of ordinary skill would not look to Silverman as motivation to modify compound 12 of Barden to arrive at the claimed invention.

As described above, Barden fails to provide any motivation or objective reason to select and/or modify compound 12 to arrive at the claimed invention. Further, the claimed compounds possess superior properties relative to compound 12 of Barden. Finally, Silverman provides no motivation or objective reason to modify compound 12 of Barden to arrive at the claimed invention. Thus, Applicants submit that the combination of Barden and Silverman does not render claims 1, 7, 11, 23-25 and 67 obvious. Applicants request reconsideration and withdrawal of the rejection.

35 U.S.C. §112

Claim 32 has been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The Examiner has stated that support for claim 32 is insufficient because there is no specific recitation of such subject matter. Applicants traverse.

Solely in an effort to further prosecution, Applicants have amended claim 32 to recite R^{9a} comprises the group  . Support for this claim can be found, *e.g.*, on page 7, lines 11-14 of the application as filed. Applicants submit that the specification describes the claimed invention in sufficient detail such that a skilled artisan would conclude that Applicants had possession of the claimed invention at the time the application was filed. Applicants request reconsideration and withdrawal of the rejection.

Claim Objections

The Examiner has noted that claims 4, 6, 9, 10, 13, 14, 19, 21, 82, 103, 109 and 110 are objected to for being dependent upon a rejected base claim or reading on subject matter beyond the restricted scope of the elected species. Applicants request reconsideration of the rejected base claim (*i.e.*, claim 1) as described *supra*. Applicants further request reconsideration of claims 4, 6, 9, 10, 13, 19, 21, 82, 103, 109 and 110 upon a finding of patentability of the generic claims presented herein.

CONCLUSION

Applicants respectfully submit that this application is in condition for allowance. If there are any questions regarding this amendment and/or these remarks, the Examiner is respectfully requested to telephone the Applicants' attorney/agent undersigned.

Respectfully submitted,

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